Kardiologia Polska 2018; 76, 5: 830–837; DOI: 10.5603/KP.a2018.0092 ISSN 0022–9032

REVIEW

Reperfusion treatment in acute myocardial infarction in elderly patients

Frans Van de Werf

Department of Cardiovascular Sciences, KU Leuven, Belgium

Abstract

In this paper the current knowledge of reperfusion therapy in elderly patients with an ST-segment elevation acute myocardial infarction (STEMI) is summarised. Placebo-controlled trials of fibrinolytic agents, direct comparative trials of fibrinolytic agents and antithrombotic co-therapies, and randomised trials of primary percutaneous coronary intervention (PCI) versus fibrinolytic therapy as well as registries are briefly reviewed, focusing on the impact of age. The benefit and risk of a combined pharmacological and mechanical approach is presented. Important differences between a "facilitated PCI" and a "pharmaco-invasive strategy", particularly in older STEMI patients, are highlighted. It will become clear at the end of this review that the knowledge about the benefit and risk of reperfusion therapy in the elderly is still incomplete and that more clinical trials in the elderly are needed. Practical recommendations for elderly patients with STEMI based on the current knowledge have been provided.

Key words: ST-segment elevation myocardial infarction, fibrinolysis, primary percutaneous coronary intervention, elderly

Kardiol Pol 2018; 76, 5: 830–837

INTRODUCTION

It is well-known that, especially in developed countries, the relative proportion of elderly patients with acute coronary syndromes is constantly increasing. In this regard it is amazing how little data we have on the optimal reperfusion treatment and outcomes of elderly patients who experience ST-segment elevation acute myocardial infarction (STEMI). Important questions have to be addressed but, unfortunately, answers are not available for all of them.

IS REPERFUSION WITH FIBRINOLYTIC AGENTS LIVE-SAVING IN THE ELDERLY?

The discussion of whether reperfusion (with fibrinolytic agents) is live-saving in STEMI patients aged 75 years or older started with the publication of the meta-analysis by the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group in *Lancet* in 1994 (Fig. 1) [1]. In this meta-analysis of randomised, placebo-controlled trials the effect of fibrinolytic therapy on 35-day mortality in this age group was not significant (24.3% in subjects with fibrinolytic therapy vs. 25.3% in subjects without this therapy). However, a subsequent re-analysis of the results of this database in which elderly (aged 75 years or older), admitted with STEMI or new (or presumed to be new) left branch bundle block within 12 h of the symptom onset, were analysed, showed a significant 15% reduction of 35-day mortality with lytic therapy (Fig. 2). Registry data published around that time were also controversial. A Medicare analysis of 7864 patients ranging between 65 and 86 years of age raised concerns about the appropriateness of using fibrinolysis in the elderly after observing no survival benefit in patients above 75 years of age [2]. The apparent excess in mortality observed in this registry was probably due to a negative selection bias, i.e. fitter elderly patients might have been more amenable to percutaneous coronary intervention (PCI), and a substantial portion of elderly patients receiving fibrinolytic therapy had one or more contraindications. Another observational study showed that of 719 elderly STEMI patients eligible for fibrinolytic therapy, only 63% actually received it, while 27% of patients with an absolute contraindication nevertheless received this therapy [3]. Such observational data underscore the complexity of interpreting outcomes given their confounding nature but were certainly not helpful in convincing cardiologists to give fibrinolytic therapy to elderly STEMI patients. By contrast, in another much larger analysis of 37,983 Medicare patients above 65 years of age, fibrinolytic therapy resulted in a reduction in one-year mortality that was

Address for correspondence:
Frans Van de Werf, MD, PhD, Department of Cardiovascular Sciences, KU Leuven, Belgium, e-mail: frans.vandewerf@uzleuven.be
Received: 04.04.2018 **Accepted:** 04.04.2018 **Available as AoP:** 06.04.2018

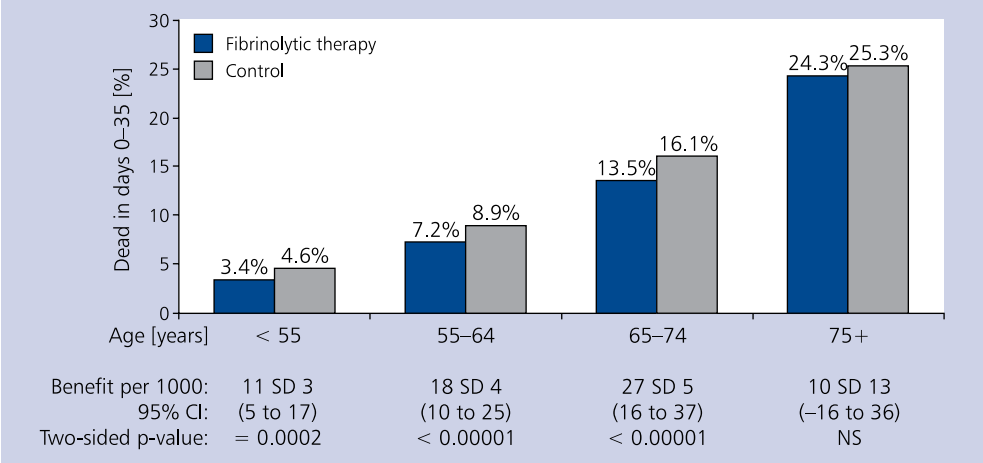

Figure 1. Age-related outcomes in placebo-controlled trials with fibrinolytic agents included in the analysis of Fibrinolytic Therapy Trialists' (FTT) collaboration [1]; CI — confidence interval; NS — not significant; SD — standard deviation

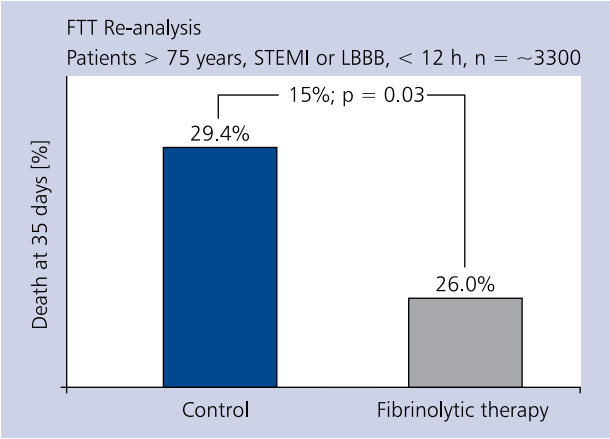

Figure 2. Re-analysis of outcomes in the elderly from the Fibrinolytic Therapy Trialists' (FTT) data base; LBBB — left bundle branch block; STEMI — ST-segment elevation myocardial infarction

comparable to primary PCI [4]. Similarly, in a Swedish registry, a propensity-adjusted analysis also demonstrated a significant improvement in survival in patients over the age of 74 years [5]. It is also important to realise that patients with prior stroke have often been included in registries and even clinical trials [6]. The apparent hazard conferred by fibrinolytic therapy in this context has been insufficiently addressed to date and has contributed — in the author's view — to an unbalanced assessment of the role of fibrinolysis as a treatment option for the elderly.

It was hoped that fibrin-specific agents such as tissue-type plasminogen activator (tPA, alteplase) would not only be more effective but also safer because of the local action on the fibrin clot and the absence of a plasma lytic state. This is unfortunately not the case. In all studies with fibrin-selective agents there was an excess of intracranial haemorrhages when compared with streptokinase, a non-fibrin specific agent. However, because of a greater effectiveness for clot lysis (and thus for reperfusion) the "net clinical benefit" favoured the fibrin-specific agents. This was most clearly demonstrated in the large Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial with accelerated infusion of alteplase performed in more than 40,000 STEMI patients [7]. Different variants of alteplase have been developed subsequently with the aim of increasing the fibrin-specificity of the agent and decreasing the plasma clearance of the molecule so that the agent could be given as a bolus. Tenecteplase, developed by Genentech Inc. (South San Francisco, CA, USA), is the most successful alteplase variant. It can be given as a single bolus and is more fibrin-specific than alteplase. In different large-scale comparative studies it became clear that the higher the fibrin-specificity of an agent, the lower the risk of non-intracranial bleedings (tenecteplase < alteplase > < streptokinase). The early phase trials assessing the efficacy and safety of single-bolus tenecteplase used fixed, not weight-adjusted, doses of the agent. Several subsequent patency and pharmacokinetic analyses from these trials examined the relationship between body-weight, dose, and benefit versus risk. With increasing weight (i.e. lower weight-adjusted dose), the rate of successful reperfusion appeared to decrease incrementally. Above a weight-adjusted dose of about 0.5 mg/kg, there was no improvement in Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow rates, whereas below this dose, patency rates decreased significantly. The opposite was seen for major bleeding complications. In the end, a 10-kg tiered, weight-adapted dose of tenecteplase was chosen for the phase 3 programme [8]. In the double-blind Assessment of the Safety and Efficacy of

a New Thrombolytic (ASSENT-2) trial, 16,949 patients were randomised to the single bolus weight-adapted tenecteplase or weight-adjusted front-loaded alteplase [9]. Specifically designed as an equivalence trial, this study showed that tenecteplase and alteplase were equivalent for 30-day mortality. The two treatments did not differ significantly in any subgroup analysis, including the elderly, except for lower 30-day mortality with tenecteplase in patients treated 4 h after symptom onset. Although the overall rates of intracranial haemorrhage were almost identical for tenecteplase (0.93%) and alteplase (0.94%), it was noted that female patients, the elderly (> 75 years), and patients weighing less than 67 kg tended to have lower rates of intracranial bleeding after tenecteplase treatment. Nevertheless, in spite of a weight-adjusted dose for both fibrinolytic agents, more intracranial bleedings were observed in patients with lower body weight and among the elderly. There was a clear age-related increase in intracranial haemorrhage rate: 0.75% in patients between 63 and 67 years old, 1.57% in patients between 68 and 72 years old, 2.03% in patients between 73 and 78 years old, and 2.22% in patients above 78 years old. Tenecteplase tended to have fewer intracranial haemorrhages (1.72%) than alteplase (2.62%) in patients older than 75 years, but this difference was not significant.

WHICH ANTITHROMBOTIC CO-THERAPY SHOULD BE GIVEN WITH FIBRINOLYTIC AGENTS?

More potent inhibition of platelet aggregation by clopidogrel, on top of aspirin, further reduces the risk of early thrombotic complications (reocclusion). In the large ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), 45,852 Chinese patients with possible myocardial infarction (including 11,934 above the age of 70 years) were randomised to placebo or 75 mg of clopidogrel daily, without a loading dose [10]. Clopidogrel was found to be associated with significant reduction in the risk of the two co-primary endpoints, in-hospital death, reinfarction or stroke (–9%), and all-cause mortality (–7%). This benefit was consistent across all age groups, including the 55% of patients treated with fibrinolysis (not all patients had STEMI). The incidence of intracranial and major non-intracranial bleeding was low, and not different between the two treatment arms. Importantly, there was no excess of intracranial or major bleeding in the elderly or in fibrinolytic-treated patients. In the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY–TIMI 28) trial, which compared clopidogrel (300 mg loading dose and maintenance dose of 75 mg/day) with placebo in fibrinolytic-treated STEMI patients, no individuals above 75 years of age were studied [11]. No excess in intracranial haemorrhage was found in patients in the clopidogrel arm. Whereas a loading dose of 300 mg of clopidogrel was given upfront with tenecteplase, followed by a daily dose of 75 mg in the Strategic Reperfusion Early after Myocardial Infarction (STREAM) study (see pharmaco-invasive strategy below), no loading dose was given in patients ≥ 75 years because of a lack of safety data, both before and after halving the dose of tenecteplase during the trial [12]. However, it remains uncertain whether an upfront loading dose of clopidogrel is necessary in the elderly now that half-dose tenecteplase appears to yield a favourable risk/benefit ratio in these patients (see below). In the author's view, the addition of an upfront loading dose of a $P2Y_{12}$ inhibitor in elderly STEMI patients receiving a pharmaco-invasive reperfusion requires further study. It is important to note that the newer $P2Y_{12}$ antagonists (ticagrelor, prasugrel, cangrelor) have not been studied together with fibrinolytic agents. In the recently published Ticagrelor in Patients With ST Elevation Myocardial Infarction Treated With Pharmacological Thrombolysis (TREAT) study in patients < 76 years, ticagrelor was given on average 11.4 h after administration of the lytic and did not result in a benefit over clopidogrel on 30-day outcomes [13]. There was a significantly higher incidence of minor bleeding complications up to 30 days in the patients allocated to ticagrelor.

Fibrin-specific fibrinolytics require additional anticoagulation, and the optimal anticoagulant and dosing for elderly patients has long been a matter of debate. An age-adjusted dose of enoxaparin was evaluated in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)-TIMI 25 study: no bolus and 0.75 mg/kg twice daily in patients ≥ 75 years, versus the standard 30 mg intravenous loading bolus followed by 1 mg/kg bid in younger patients [14]. Age-adjusted enoxaparin increased the risk of major bleeding but not the risk of intracranial haemorrhage after fibrinolytic therapy, as compared to unfractionated heparin, while still reducing the risk of ischaemic complications. The increased risk of non-intracranial bleeding complications was offset by a significant reduction of ischaemic events, however, resulting in an 18% improvement in net clinical benefit compared with unfractionated heparin. Since ExTRACT, age-adjusted enoxaparin has been the recommended anticoagulant accompanying fibrin-specific fibrinolytics.

In conclusion, it is now well-accepted and clearly recommended in all guidelines that reperfusion therapy with fibrinolytic agents is effective in elderly patients with STEMI admitted within 12 h of symptom onset. In the most recent European Society of Cardiology (ESC) guidelines, weight-adjusted single bolus tenecteplase together with enoxaparin (no intravenous bolus) and clopidogrel (no loading dose) is recommended as the preferred fibrinolytic treatment [15]. The question remains: which is the best reperfusion therapy in the elderly (fibrinolysis or primary PCI), and does one size fit all?

WHICH REPERFUSION THERAPY WORKS BEST IN THE ELDERLY?

Only a limited number of trials have compared fibrinolytic therapy with primary PCI in elderly patients in a prospective randomised manner. The oldest and, surprisingly, also

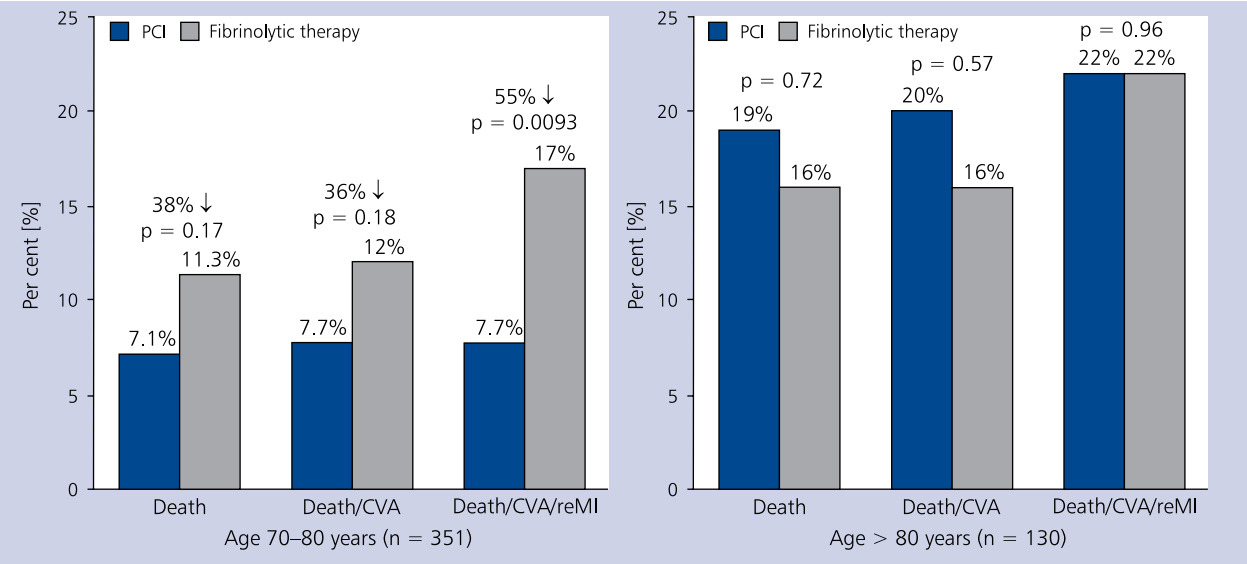

Figure 3. Age-related outcomes of Senior PAMI comparing fibrinolytic therapy with primary percutaneous coronary intervention (PCI) in the elderly [16]; CVA — cardiovascular adverse events; reMI — re-infarction

the largest study is the Primary Angioplasty in Myocardial Infarction (SENIOR-PAMI) trial. In this study 483 patients above the age of 70 years were randomised to lytic therapy or primary PCI. Randomisation was stratified according to age category: from 70 to 80 and > 80 years of age. Data were available from 481 patients. In the first age category there was a numerically lower incidence of death or death plus stroke at 30 days in the primary PCI group. When re-infarction was added to the combined endpoint the difference became significant (7.7% vs. 17%, p = 0.0093). Surprisingly, in patients older than 80 years this combined endpoint was identical in the two groups (22%) and the rates of death and death plus stroke were numerically higher in the primary PCI group (Fig. 3). This study was presented in 2005 at a Transcatheter Cardiovascular Therapeutics meeting but, to the author's knowledge, it has never been published [16]. A later, prospective randomised study, the TRIANA trial, had to be stopped prematurely because of lack of recruitment [17]. Data on 266 STEMI patients above the age of 75 years were analysed. The mean age was 81 years. The primary endpoint was the composite of all-cause death, re-infraction, or disabling stroke at 30 days. This was reached in 18.9% of the patients allocated to primary PCI and in 25.4% of those allocated to fibrinolytic therapy (odds ratio 0.69 [0.38–1.2], p = 0.21). No differences in total mortality were observed between the two treatments.

Regarding observational studies, an important paper analysing and summarising the results of the different trials was published in 2005 [18]. Overall, the data from that analysis suggested a better outcome with primary PCI than with thrombolytic therapy (Fig. 4). In conclusion, there is evidence that primary PCI is better than lytic therapy also in the elderly, although convincing studies are lacking.

PRIMARY PCI FOR ALL ELDERLY STEMI PATIENTS?

The time delay from the ESC diagnosis of STEMI to the start of reperfusion by PCI is often underestimated for several reasons, especially in the elderly. Atypical presentation is an important reason why the diagnosis of STEMI is often delayed in elderly patients. On screening in an emergency department, the elderly with atypical symptoms are often considered as less urgent cases. When it comes to estimating the delay between diagnosis based on electrocardiogram (ECG) and PCI-mediated reperfusion, the recent ESC guidelines define "crossing the lesion with the guide wire" as "start of reperfusion". As shown in Figure 5 there are many steps (time delays) to be taken into account besides the transport of a patient to a PCI hospital. These delays may explain the gap between estimated and real time delays. For example, in a large United States registry of 22,481 patients the median estimated inter-hospital drive time was 57 min (interquartile range, 36–88 min). When the estimated drive time exceeded 30 min, only 42.6% of transfer patients treated with primary PCI achieved the first door (of the community hospital)-to-balloon time within 120 min [19].

A PHARMACO-INVASIVE STRATEGY?

An important recent development has been the concept of a pharmaco-invasive strategy, the components of which are early fibrinolysis in conjunction with rescue PCI in patients with fibrinolytic failure and subsequent early angiography/PCI in those with lytic success. A key feature of this strategy is that

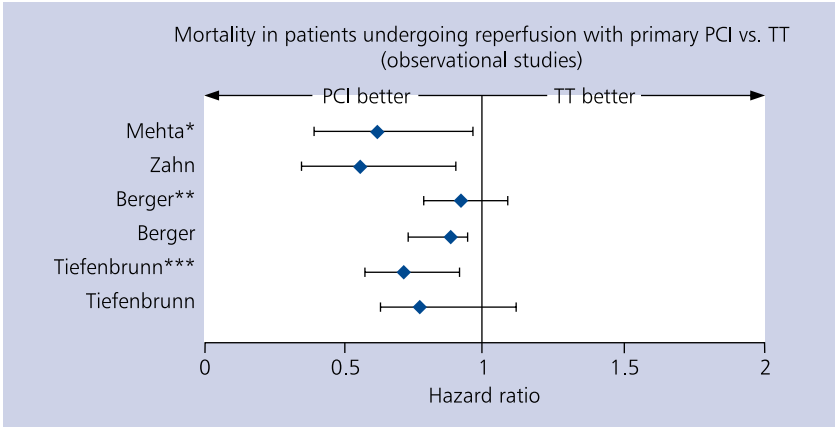

Figure 4. Summary of registry data comparing fibrinolytic therapy with primary percutaneous coronary intervention (PCI) [18]; TT — thrombolytic therapy. *In-hospital mortality; **for ideal patients; ***combined in-hospital mortality and stroke in patients with acute myocardial infarction without shock

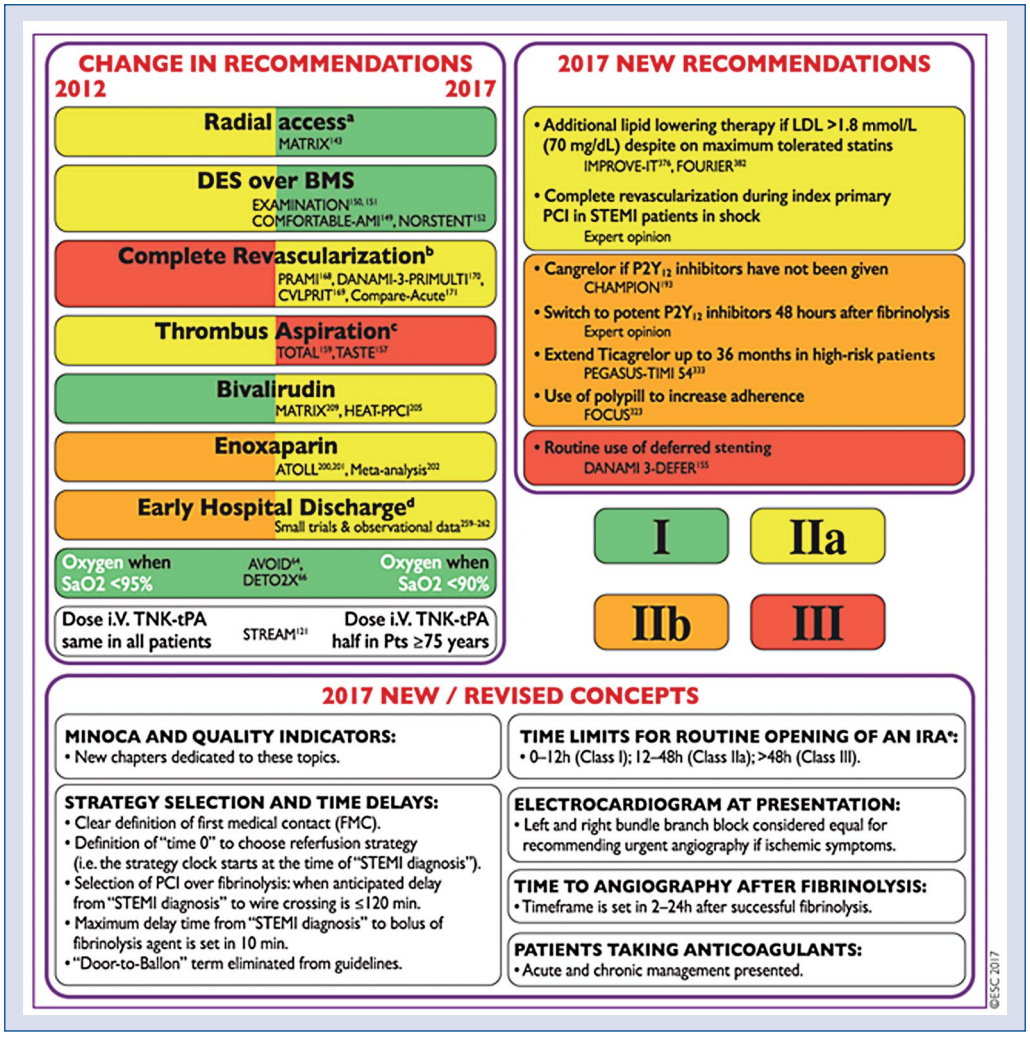

Figure 5. Summary of changes made in the 2017 European Society of Cardiology STEMI guidelines [15]; abbreviations — see the original article [15]

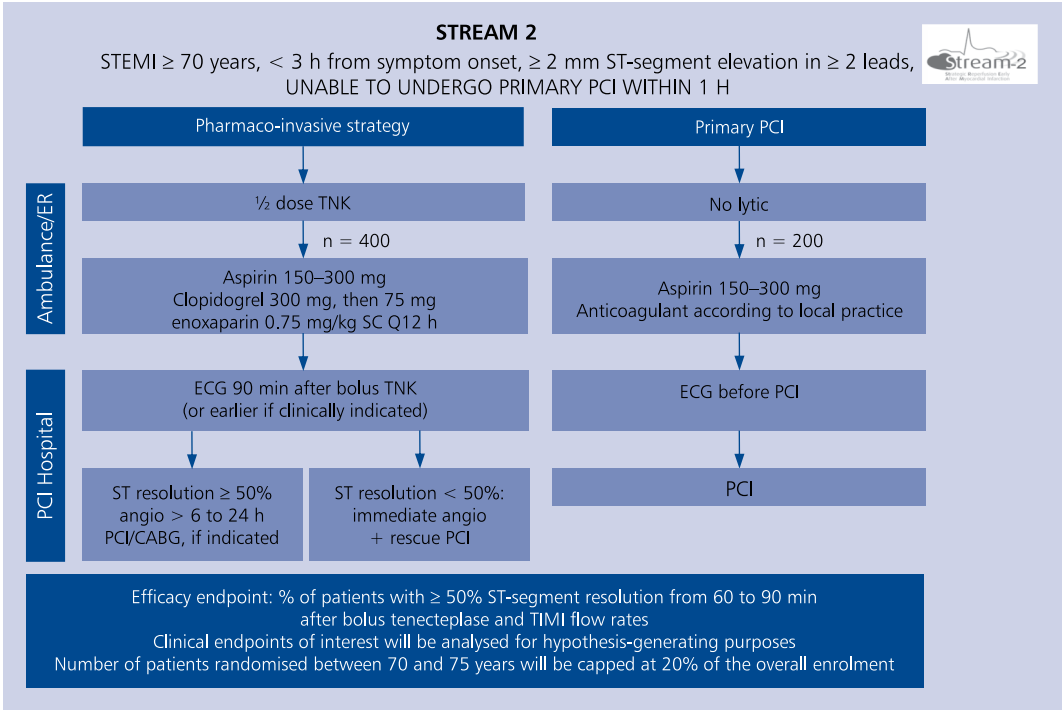

Figure 6. Design of STREAM-2 trial [KU Leuven, Belgium]; angio — coronary angiography; CABG — coronary artery bypass grafting; ECG — electrocardiogram; ER — emergency room; STEMI — ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; TIMI — Thrombolysis in Myocardial Infarction; TNK — tenecteplase

fibrinolytic therapy is given in the ambulance or the emergency department of the community hospital, and that the patient is then immediately transferred to the PCI hospital (without waiting for the result of the fibrinolytic treatment). On arrival at the PCI hospital (preferably a cath lab) a second ECG is taken, and when there is evidence of successful lysis (e.g. > 50% ST-segment resolution) no immediate coronary angiography is performed. The reason why the invasive procedure is delayed by at least 2 to 3 h is to avoid any possible pro-thrombotic effect of the lytic agent. In case of failed fibrinolysis rescue PCI must be performed immediately. It is very important that a so-called "facilitated PCI" is clearly differentiated from primary PCI. In a facilitated PCI strategy the decision to perform immediate PCI is made as soon as the diagnosis. Lytic therapy is given to mitigate the so-called PCI-related delay. The coronary angiography/PCI is performed immediately on arrival in the cath lab, regardless of the outcome of the preceding fibrinolytic therapy. As shown in multiple studies, facilitated PCI does not provide any benefit over primary PCI. The key study comparing a pharmaco-invasive strategy with standard primary PCI is the STREAM-1 study [12]. In this analysis of 1892 STEMI patients who could not be treated with primary PCI within 1 h of the first medical contact, the pharmaco-invasive strategy with tenecteplase, enoxaparin, and clopidogrel was at least as good as primary PCI for the primary endpoint of death, shock, congestive heart failure, or reinfarction at 30 days. However, after approximately one-fifth of the planned STREAM population had been enrolled, the tenecteplase bolus was halved in patients ≥ 75 years of age because of an excess of intracranial haemorrhages in this age group. Before reducing the dose of tenecteplase, three out of 42 (7.1%) lytic-treated elderly patients experienced an intracranial haemorrhage, and two of these were fatal. This change was induced by a successful strategy of half-dose tenecteplase followed by immediate transfer applied in STEMI patients presenting to rural hospitals in Minnesota [20]. In this prospective registry, all patients diagnosed with STEMI beyond 60 miles from the PCI centre (n = 839, 160 ≥ 75 years) received half-dose tenecteplase, in association with 600 mg of clopidogrel, irrespective of age. The strategy appeared to be both effective and safe: only two patients experienced an intracranial bleeding, and the pre-PCI patency (TIMI grade 2/3) was an impressive 74%. After implementing the dose reduction in STREAM, not a single additional intracranial bleeding or stroke was observed in the subsequent 97 patients above the age of 75 years randomised into the pharmaco-invasive arm. The efficacy in reperfusion of half a bolus of tenecteplase in these elderly patients was assessed by evaluating the extent of ST-segment resolution ≥ 50% on post-treatment ECG at 60 to 90 min, and was found to be similar before and after the amendment [20]. Similarly, the percentage of lytic-treated elderly patients requiring rescue PCI was comparable before versus after halving the dose (43% vs. 44%). In addition, the primary composite endpoint was numerically lower after

the amendment (25% vs. 31% before). Taken together, these observations suggest that a half-dose bolus tenecteplase in association with the currently recommended anti-thrombotic concomitant therapy appears to be safer but is still efficacious for elderly patients. However, more definitive prospective data are required in an adequately powered randomised clinical trial. Such a study, STREAM-2, is currently ongoing and analyses elderly patients (≥ 70 years old) with STEMI, randomised within 3 h of onset of symptoms. It aims to compare the efficacy and safety of two strategies, according to local standards: early fibrinolytic treatment with half-dose tenecteplase, additional antiplatelet therapy with aspirin and a loading dose of 300 mg of clopidogrel coupled with enoxaparin, followed by coronary angiography within 6 to 24 h or rescue coronary intervention, as required, and standard primary PCI with a $P2Y_{12}$ antagonist and antithrombin treatment (Fig. 6).

CONCLUSIONS AND PRACTICAL RECOMMENDATIONS

Despite evidence that fibrinolytic therapy improves outcomes irrespective of age, many elderly STEMI patients remain undertreated or subject to major delays to primary PCI, in part because of concerns about bleeding risk associated with this type of therapy. Curiously, while age-specific dose reductions have been made to concomitant antithrombotic drugs such as clopidogrel and enoxaparin, until recently no dose-adjustments have been made in the case of the fibrinolytic agents in the elderly. In the pharmaco-invasive STREAM-1 trial, halving the bolus of tenecteplase for patients above 75 years of age because of an unacceptably high intracranial bleeding rate in the elderly receiving a full dose of tenecteplase (after including about 20% of the total population) was associated with a more favourable safety/efficacy profile. An ongoing STREAM-2 trial aims to assess whether a pharmaco-invasive strategy including half-dose tenecteplase, age- and weight-adjusted enoxaparin, and clopidogrel, followed by routine coronary angiography represents a safe and efficacious alternative reperfusion therapy for elderly patients.

In the meantime, the following strategies should be recommended in patients ≥ 75 years old (based on the 2017 ESC STEMI guidelines) (Fig. 5) [15]:

— primary PCI is recommended in all STEMI patients up to 12 h after onset of symptoms if crossing the wire of the culprit lesion can be performed within 120 min of the ECG diagnosis;

— if the above is not possible, immediate fibrinolytic therapy should be given. The preferred pharmacological cocktail is half-dose of tenecteplase, enoxaparin 0.75 mg/kg (no loading, max 75 mg), 75 mg clopidogrel (no bolus), plus 150 to 300 mg of aspirin. After administration, patients should be immediately transferred to the PCI hospital.

According to the guidelines, patients < 75 years old should be treated with full-dose tenecteplase, an additional intravenous bolus of enoxaparin, and a loading dose of 300 mg of clopidogrel. Obviously this 75-year cut-off age is artificial and does not take into account biological age and comorbidities. It is known that the bleeding risk in fibrinolytic therapy generally starts to increase around the age of 60 years. Giving frail STEMI patients between the age of 60 and 75 years a reduced dose of the fibrinolytic cocktail (as explained above) is worth considering, especially if a back-up option of a cath lab is available in case the administered reduced dose of the fibrinolytic cocktail fails. In this regard, a recent pharmaco-invasive study (Early Routine Catheterisation After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment-Elevation Myocardial Infarction [EARLY-MYO]) in Chinese STEMI patients < 76 years of age supports this recommendation. This study showed favourable results with half-dose alteplase in comparison to standard primary PCI in STEMI patients who could not be treated with primary PCI within 1 h. No intracranial haemorrhages were observed, and there was even evidence of better tissue reperfusion in those allocated to the pharmaco-invasive strategy [21].

Conflict of interest: *Frans Van de Werf has been the chair of multiple randomised trials in STEMI patients sponsored by different pharmaceutical companies, including Boehringer Ingelheim, SANOFI, The Medicines Company, Novartis, and Merck.*

References

1. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet. 1994; 343(8893): 311–322, indexed in Pubmed: 7905143.
2. Thiemann DR, Coresh J, Schulman SP, et al. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. Circulation. 2000; 101(19): 2239–2246, indexed in Pubmed: 10811589.
3. Soumerai SB, McLaughlin TJ, Ross-Degnan D, et al. Effectiveness of thrombolytic therapy for acute myocardial infarction in the elderly: cause for concern in the old-old. Arch Intern Med. 2002; 162(5): 561–568, indexed in Pubmed: 11871924.
4. Berger AK, Radford MJ, Wang Y, et al. Thrombolytic therapy in older patients. J Am Coll Cardiol. 2000; 36(2): 366–374, indexed in Pubmed: 10933344.
5. Stenestrand U, Wallentin L. Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). Fibrinolytic therapy in patients 75 years and older with ST-segment-elevation myocardial infarction: one-year follow-up of a large prospective cohort. Arch Intern Med. 2003; 163(8): 965–971, doi: 10.1001/archinte.163.8.965, indexed in Pubmed: 12719207.
6. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med. 2003; 349(8): 733–742, doi: 10.1056/NEJMoa025142, indexed in Pubmed: 12930925.
7. White HD, Barbash GI, Califf RM, et al. Age and outcome with contemporary thrombolytic therapy. Results from the GUSTO-I trial. Global Utilization of Streptokinase and TPA for Occluded coronary arteries trial. Circulation. 1996; 94(8): 1826–1833, indexed in Pubmed: 8873656.

8. Wang-Clow F, Fox NL, Cannon CP, et al. Determination of a weight-adjusted dose of TNK-tissue plasminogen activator. Am Heart J. 2001; 141(1): 33–40, doi: 10.1067/mhj.2001.112092, indexed in Pubmed: 11136484.
9. Van De Werf F, Adgey J, Ardissino D, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Lancet. 1999; 354(9180): 716–722, indexed in Pubmed: 10475182.
10. Chen ZM, Jiang LX, Chen YP, et al. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005; 366(9497): 1607–1621, doi:10.1016/S0140-6736(05)67660-X, indexed in Pubmed: 16271642.
11. Sabatine MS, Cannon CP, Gibson CM, et al. CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005; 352(12): 1179–1189, doi: 10.1056/NEJMoa050522, indexed in Pubmed: 15758000.
12. Armstrong PW, Gershlick AH, Goldstein P, et al. STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2013; 368(15): 1379–1387, doi: 10.1056/NEJMoa1301092, indexed in Pubmed: 23473396.
13. Berwanger O, Nicolau JC, Carvalho AC, et al. Writing Committee for the TREAT Study Group. Ticagrelor vs Clopidogrel After Fibrinolytic Therapy in Patients With ST-Elevation Myocardial Infarction: A Randomized Clinical Trial. JAMA Cardiol. 2018 [Epub ahead of print], doi:10.1001/jamacardio.2018.0612, indexed in Pubmed: 29525822.
14. Antman EM, Morrow DA, McCabe CH, et al. ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med. 2006; 354(14): 1477–1488, doi: 10.1056/NEJMoa060898, indexed in Pubmed: 16537665.
15. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177.
16. Grines C. SENIOR PAMI: a prospective randomized trial of primary angioplasty and thrombolytic therapy in elderly patients with acute myocardial infarction. Presented at: Transcatheter Cardiovascular Therapeutics 2005; October 19, 2005; Washington, DC. 2005.
17. Bueno H, Betriu A, Heras M, et al. TRIANA Investigators. Primary angioplasty vs. fibrinolysis in very old patients with acute myocardial infarction: TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) randomized trial and pooled analysis with previous studies. Eur Heart J. 2011; 32(1): 51–60, doi: 10.1093/eurheartj/ehq375, indexed in Pubmed: 20971744.
18. Mehta RH, Granger CB, Alexander KP, et al. Reperfusion strategies for acute myocardial infarction in the elderly: benefits and risks. J Am Coll Cardiol. 2005; 45(4): 471–478, doi: 10.1016/j.jacc.2004.10.065, indexed in Pubmed: 15708688.
19. Vora AN, Holmes DN, Rokos I, et al. Fibrinolysis use among patients requiring interhospital transfer for ST-segment elevation myocardial infarction care: a report from the US National Cardiovascular Data Registry. JAMA Intern Med. 2015; 175(2): 207–215, doi: 10.1001/jamainternmed.2014.6573, indexed in Pubmed: 25485876.
20. Larson DM, Duval S, Sharkey SW, et al. Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. Eur Heart J. 2012; 33(10): 1232–1240, doi: 10.1093/eurheartj/ehr403, indexed in Pubmed: 22041553.
21. Pu J, Ding S, Ge H, et al. EARLY-MYO Investigators. Efficacy and Safety of a Pharmaco-Invasive Strategy With Half-Dose Alteplase Versus Primary Angioplasty in ST-Segment-Elevation Myocardial Infarction: EARLY-MYO Trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment-Elevation Myocardial Infarction). Circulation. 2017; 136(16): 1462–1473, doi: 10.1161/CIRCULATIONAHA.117.030582, indexed in Pubmed: 28844990.

Cite this article as: Van de Werf F. Reperfusion treatment in acute myocardial infarction in elderly patients. Kardiol Pol. 2018; 76(5): 830–837, doi: 105603/KP.a2018.0092.